REMARKS

Upon entry of the present amendment, claims 1-17 and 46-49 will be pending. Applicants have amended claim 7 to insert the word "claim," and claims 11-13 to add a period that was inadvertently omitted from the end of each of those claims. Claims 1-3 and 5 have also been amended to specify a mammalian ΔTRα2 polypeptide; claim 3 has been further amended to recite a cell expressing a mammalian ΔTRα2 polypeptide. Applicants have also added new claims 46-49. Support for the new claims can be found throughout the specification as filed, e.g., at page 1, lines 22-23, and at page 11, lines 5-13.

Applicants submit herewith a substitute sequence listing, adding the human ΔTRα2 nucleic acid and polypeptide sequences (SEQ ID NOs:4 and 5), which were incorporated by reference in the specification as filed at page 1, lines 21-23. The specification refers specifically to Chassande et al., Mol. Endocrinol. 11:1278-1290 (1997), which describes the identification of ΔTRα2, which includes exons 8-10 of the full length TRα2 receptor. Chassande et al. at page 1279, legend to Figure 1, notes that the gene structure of TRα2 was described in Laudet et al. (Nuc. Acids. Res. 19(5):1105-1112 (1991) (copy enclosed). The two sequences added by this amendment are the material previously incorporated by reference (i.e., the sequences of exons 8-10 identified by Chassande et al.) and thus the amendment contains no new matter. See MPEP 608.01(p); 37 CFR 1.57(f); *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In addition, the specification has been amended to remove hyperlinks.

No new matter has been added.

Objections to the Specification

The specification was objected to at page 2 of the Office Action of February 27, 2007, (referred to herein as the "Office Action"), for including embedded hyperlinks. As noted above, the specification has been amended to remove hyperlinks. Applicants believe that there are no other hyperlinks present in the application.

In addition, the specification was objected to for allegedly lacking a descriptive title. A new title is provided herein.

Finally, applicants have amended the first paragraph of the specification to update the status of the prior application, which issued as U.S. Patent No. 6,730,472.

In light of these amendments, Applicants request withdrawal of the objections to the specification.

Claim Objections

Claims 11-13 were objected to for failing to end in a period. This has been corrected by the present amendment, and Applicants therefore request withdrawal of the objections to the claims.

Claim rejections – 35 U.S.C. § 112, First Paragraph, Written Description

The Office Action rejected claims 1-17 as lacking adequate written description. According to the Office Action at page 3,

> [c]laims 1-17 are directed to methods of identifying a candidate compound that modulates ΔTRα2 polypeptide activity comprising contacting a ΔTRα2 polypeptide with a test compound and assaying for binding or activity. The specification indicates that a ΔTRα2 polypeptide was synthesized by cell-free translation of appropriate segments of the rat ΔTRα2 cDNA. However, the specification does not indicate what the appropriate segments were. Also, the term "a ΔTRα2 polypeptide" as recited in the claims encompasses far more than just rat ΔTRα2 polypeptide.

Applicants respectfully traverse.

Applicants note that there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure. *Falkner v. Inglis*, 448 F.3d 1357, 1367 (Fed. Cir. 2001). The Federal Circuit has recently affirmed that the sequence structure of each gene in a gene family need not be recited if the sequences of multiple genes in the family are known in the art and if the members of the gene family share significant homologies from one species to another. *Invitrogen v. Clontech*, 429 F.3d 1052 (Fed. Cir. 2005).

As noted above, claims 1-3 and 5 have been amended to specify a mammalian ΔTRα2 polypeptide. A number of such polypeptides are described in the specification and were known in the art at the time of filing.

The specification at page 1, lines 18-19, cites Chassande et al., (Mol. Endocrinol. 11:1278-1290 (1997); copy previously submitted), which describes the identification of transcripts initiated from an internal transcription site in exon 7 of TRα2 (a variant of the T3 thyroid hormone receptor). One of these truncated transcripts, which as noted in the specification (see page 11, lines 1-12) includes exons 8-10, was termed ΔTRα2. Figure 4 of Chassande et al. provides a schematic representation of the intron/exon structure of these transcripts.

Chassande et al. also provides an Accession No. for exon 10 of human TRα2 (EMB X55066, first seen at NCBI on April 21, 1993) (see page 1281). Laudet et al. (Nuc. Acids. Res. 19(5):1105-1112 (1991)), also cited in Chassande et al., sets forth the full genomic organization of the human c-erbA-1 gene (which encodes both TRα1 and TRα2), including the sequences of each of the exons with their translation.

Further, the present specification at page 11, lines 10-11, itself indicates that "[n]ucleic acid sequences that encode... ΔTRα2 are known for some species," and provides exemplary sequences, including NCBI Accession No. X07751 for a cDNA encoding mouse TRα2 (as noted above, first seen at NCBI on April 21, 1993) and NCBI Accession No. X07409 (first seen at NCBI on April 21, 1993) for a cDNA encoding rat TRα2.

The amino acid and nucleic acid sequences of a number of mammalian TRα2 (full length) polypeptides were known in the art at the time of filing, including mouse, rat, and human, see, e.g., GenBank Acc. No. NM_003250, first seen at NCBI on March 24, 1999 (human); GenBank Acc. No. M31174, first seen at NCBI on April 27, 1993 (rat); and GenBank Acc. No. X07751, first seen at NCBI on April 21, 1993 (mouse). The sequences of exons 8 and 9 were available at GenBank Acc. Nos. X55069 and X55068, respectively (both were first seen at NCBI on Apr 21 1993).

Using the BLAST program at ncbi.nlm.nih.gov, the sequences of human ΔTRα2 were compared with the mouse and rat genomes. The results indicated a high amount of homology: the nucleic acids had 88% identity for human x mouse, and 89% for human x rat; the amino acid sequences had even higher identity, about 92-93%.

Therefore, and because satisfaction of the written description requirement requires neither recitation of sequence structure, as per *Falkner v. Inglis*, nor require recitation of the sequence structure of each gene in a gene family, as per *Invitrogen v. Clontech*, and the present specification and the knowledge in the art provided a number of exemplary sequences, applicants submit that amended claims 1-17 have ample written description support in the application as filed. Applicants therefore respectfully request that the rejection be withdrawn.

Insofar as this rejection may be applied to new claims 46-49, Applicants note that these claims specify that the ΔTRα2 polypeptide comprises an amino acid sequence that is at least 95% identical to the full length of SEQ ID NO:5 and can bind myosin.

Finally, Applicants note that the claims of the issued parent patent, U.S. Pat. No. 6,730,472, recite "a mutant ΔTRα2 translation product" or "a wild type ΔTRα2 protein;" issue of these claims is *prima facie* evidence that these terms have written description support.

For at least these reasons, Applicants submit that the pending claims have ample written description in the application as filed, and request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Claim rejections – 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-17 were rejected for allegedly lacking enablement in the specification as filed. According to the Office Action at page 6,

> ...the claims are very broad in that they encompass methods of identifying a candidate compound that modulates the activity of any ΔTRα2 polypeptide comprising contacting any ΔTRα2 polypeptide with a test compound and assaying for binding or activity. Furthermore, none of the claims require that the assay be conducted in cells.
>
> A great deal of experimentation is required, given that the specification does not provide clear guidance regarding how to make any ΔTRα2 polypeptide

which is required to practice the claimed methods. Also, there is not guidance regarding how to perform an assay on a receptor separate from the cell in which it is expressed. No working examples are provided.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Applying this law to the pending application, Applicants submit that the pending claims are amply enabled.

Claims 1 and 2 are drawn to methods for identifying a "candidate compound that modulates mammalian ΔTRα2 polypeptide activity" by determining either binding of a test compound to the mammalian ΔTRα2 polypeptide (as in claim 1) or by determining the effect of a test compound on the binding of a ligand to the mammalian ΔTRα2 polypeptide.

Claim 3 is drawn to a method of identifying a candidate compound that modulates mammalian ΔTRα2 polypeptide activity employing the steps: obtaining a test sample containing a mammalian ΔTRα2 polypeptide, incubating the test sample with a test compound, and assaying the test sample for alteration of type II 5' deiodinase (D2) activity.

Claim 5 is drawn to a method of identifying a candidate compound that modulates mammalian ΔTRα2 polypeptide activity employing the steps: obtaining a test sample containing a mammalian ΔTRα2 polypeptide, performing an actin binding assay with the test sample in the presence of a test compound, such that a test compound that alters the binding of p29 vesicles to F-actin when compared to a test sample that was not incubated with the test compound is a candidate compound.

Mammalian ΔTRα2 polypeptides

Applicants submit that the breadth of these claims is amply enabled for the term "mammalian ΔTRα2 polypeptide."

As described previously, a number of sequences for mammalian ΔTRα2 polypeptides were known in the art. In addition, one of skill in the art could readily identify other ΔTRα2 sequences useful in the claimed methods. For example, the specification provides guidance at page 8, lines 5-18:

> The nucleic acid and protein sequences described herein can be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences (such as human ΔTRα1, ΔTRα2, or myosin V amino acid or nucleic acid sequences). Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. (1990) J. Mol. Biol. 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to nucleic acid molecules useful in the invention (such as human ΔTRα1, ΔTRα2, or myosin V). BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to protein molecules useful in the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) Nucleic Acids Res. 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See http://www.ncbi.nlm.nih.gov.

Having identified these sequences, the skilled practitioner could either obtain these cDNAs, or generate the cDNAs using methods known in the art and described in the Chassande et al. reference, which is incorporated by reference in this application. As one example, the

specification provides clear guidance at page 30, lines 26-28, that ΔTRα2 polypeptides can be generated by cell-free translation using the Promega® (TNT) coupled transcription-translation kit. This kit is commercially available. Thus, not only were several mammalian ΔTRα2 polypeptides described in the specification, but obtaining others would have been no more than routine for the skilled practitioner.

At page 7, the Office Action states:

> Finally, the state of the prior art provides a structure of a human form of ΔTRα2 polypeptide (Chassande et al., 1997, Mol. Endocrinol. 11:1278-1290), but it is not clear if the instant specification's concept of a ΔTRα2 polypeptide corresponds to the prior art polypeptide of the same name.

Applicants submit that the skilled practitioner would have been aware that ΔTRα2 referred to in Chassande et al. belongs to the ΔTRα2 family, and use of such a polypeptide would fall within the scope of the present claims, particularly in light of the fact that the Chassande et al. reference is cited at page 1, lines 21-23, as a reference for the "truncated receptor transcripts... that are also transcribed from the c-erbAα locus; ΔTRα1 and ΔTRα2. (*emphasis added)* In light of this, and the knowledge of one of skill in the art, Applicants submit that one of skill in the art would readily understand that the human ΔTRα2 described in Chassande et al. is a mammalian ΔTRα2 polypeptide as recited in the present claims.

Finally, Applicants note that the claims of the issued parent patent, U.S. Pat. No. 6,730,472, recite "a mutant ΔTRα2 translation product" or "a wild type ΔTRα2 protein;" issue of these claims is *prima facie* evidence that these terms are enabled.

Cell-Free Assays

Applicants note that claim 3 has been amended herein to recite a sample comprising a cell expressing a mammalian ΔTRα2 polypeptide. With regards to independent claims 1, 2, and 5, and the claims dependent therefrom, Applicants submit that these claims need not be limited to performing assays in a cell. A number of cell-free assays are known in the art, and there is no reason to believe that the ΔTRα2 polypeptides could not be used in a cell-free assay, e.g., a binding assay, nor has the Office provided any reason to believe so. (If the Office's

concern is that the ΔTRα2 polypeptide may be a membrane protein, Chassande et al. notes that the ΔTRα2 polypeptide, referred to in that reference as p26α2, had predominantly cytoplasmic localization; see page 1283, right column, first paragraph).

In addition, the specification describes an assay that is performed using ΔTRα2 polypeptides generated by cell-free translation and occurs in a cell free system:

> The thyroid hormone displacement curves for rT_3 binding to ΔTRα1 and ΔTRα2 demonstrated that both ΔTRα1 and ΔTRα2 specifically bound from 3 to 5% of the total [^{125}I]rT3. Also, both T4 and rT3 specifically displaced [^{125}I]rT3 with K_d's of about 0.3 to 1nM. These data are identical to those for native ΔTRα2 found in astrocyte lysates. T3 did not displace [^{125}I]rT3 from either thyroid hormone receptor at concentrations up to 100 nM, consistent with the failure of T3 to initiate actin-based endocytosis or bind to TIP in astrocyte lysate. Control studies done with cell-free translated ß-galactosidase showed no specific rT3 binding. *Specification at page 30, line 29 to page 31, line 6.*

The specification describes additional cell-free assays at least at page 13, line 27 to page 15, line 10, and a number of other suitable assays are known in the art and would be familiar to one of skill in the art, and the use of such assays would be no more than routine.

For at least these reasons, Applicants submit that the pending claims are amply enabled, and request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Conclusion

In light of the amendments and arguments made herein, Applicants submit that the pending claims are allowable, and request early and favorable action thereon. If the Examiner feels that it would further prosecution of the present application, she is invited to telephone the undersigned at (617) 956-5985.

The required fees for the petition for extension of time and information disclosure statement are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07917-103002.

Respectfully submitted,

Date: Aug. 27, 2007

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